UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/867,770	05/31/2001	Richard E. Jones	018240-037	6457

7590 10/01/2002

Gerald F. Swiss, Esq.
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, VA 22313-1404

EXAMINER
MCINTOSH III, TRAVISS C

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 10/01/2002 4

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/867,770	JONES, RICHARD E.	
	Examiner	Art Unit	
	Traviss C McIntosh	1621	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

Priority

Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e) to provisional application numbers 60/208,593 filed 6/02/2000 and 60/211,969 filed 6/16/2000.

Information Disclosure Statement

Acknowledgement is made of receipt of Information Disclosure Statement filed and the references will be taken into consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

Claims 1 and 8 describe a composition as being "encapsulated in a material which is selected to be dissolution resistant at a pH of about 4 to 5 or less and to readily dissolve at a pH of greater than about 4 to 5". Describing a compound which will be used as an encapsulation material by it's function , i.e. by dissolving or not dissolving at various pH's, will not substitute for the written description of the structure of the compound. The invention should be described

in such a way as to describe what the invention is, not what the invention does. Describing an encapsulation material for a pharmaceutical composition by it's function fails to distinguish the compound from other molecules that can perform the same function.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "a composition according to claim 1... comprising about 50 to about 99.5 weight percent of the pharmaceutically acceptable excipient(s)" wherein claim one makes no reference to any excipient. There is insufficient antecedent basis for this limitation in the claim. Claim 7 would find proper antecedent basis if it depended from claim 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-5, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCarthy et al. (US Patent 5,378,693) in view of Huber et al. (US Patent 4,180,559).

The claims of the instant invention are drawn to an orally deliverable composition of 2'-deoxy-2'-(fluoromethylene)cytidine (FMdC) (0.5-50% weight of composition) for treating a neoplastic or viral disease wherein the encapsulation material is dissolution resistant at a pH of about 4-5 or less and will readily dissolve at a pH of about 4-5 or more. The composition may further comprise an excipient and the encapsulation material may be cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, poly(vinyl acetate phthalate), hydroxypropyl methylcellulose acetate succinates, and cellulose acetate phthalate/diethylphthalate. The excipient (about 50-99.5% weight of composition) may be the encapsulation material, or there may be an additional excipient in the composition. The claims of the instant application are additionally drawn to a method for enhancing the oral bioavailability of FMdC by administering the composition above to a mammal.

McCarthy et al. disclose a composition which can be used to provide treatment of a patient afflicted with a carcinoma comprising administering the compound of formula (1), (1a), or (1b) (column 23, lines 35-43). Formula 1 of McCarthy et al. (see column 1) comprises FMdC wherein X_1 is hydrogen, X_2 is a halogen (fluorine), V is oxy, and B is radical on far right comprising Y_4 (hydrogen) and Y_5 (amino) (column 1, lines 20-50). The compound of McCarthy et al. is effective in slowing, interrupting, arresting, or stopping the growth of the carcinoma in

the patient. The compound of McCarthy et al. is taught to be administered in any form or mode which makes the compound bioavailable in effective amounts, including and preferably orally. McCarthy et al. note that one skilled in the art of preparing formulations can readily select the proper form and mode of administration depending on the particular characteristics of the compound selected, the disease state of the patient to be treated, the stage of the disease, and other relevant circumstances (column 24, lines 13-27). The compound of McCarthy et al. can be administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptable excipients, wherein the proportion and nature are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. (column 24, lines 28-34). Suitable carriers or excipients to be used for the composition of McCarthy et al. are well known in the art wherein the compositions may be adapted for oral or parenteral use and may be administered in the form of tablets, capsules, suppositories, solution, suspensions, or the like (column 24, lines 1-6). For the purpose of oral therapeutic administration, the compound may be incorporated with excipients and include at least 4% of the active agent, and more particularly from between 4% - 70% (column 25, lines 10-19). The excipients taught by McCarthy et al. include starch or lactose, and disintegrating agents such as alginic acid, Primogel, and corn starch (column 25, lines 25-30). Other dosage unit forms may contain various materials which modify the physical form of the dosage unit, for example, as coatings of sugar, shellac, or other enteric coating agents (column 25, lines 37-41). What is not taught by McCarthy et al. is to use the specific encapsulation materials, such as hydroxypropyl methylcellulose phthalate as the enteric coating.

Huber et al. disclose the use of hydroxypropyl methylcellulose phthalate to protect an active agent from acid degradation in the stomach, allowing the agent to be dissolved at the pH of 5.0 to 5.5, in order to permit dissolution and absorption of the drug substance (column 2, lines 35-42) by releasing the active compound under the slightly acidic conditions of the duodenum, where the compound is available for absorption into the bloodstream (column 2, line 62 – column 3, line 2). What Huber et al. do not teach is to use FMdC as the active agent in the composition.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the protective agent of Huber et al. in combination with the compositions of McCarthy et al. because it is known that the acidic conditions in the stomach degrade compounds thereby prohibiting compounds from being absorbed by the bloodstream and in turn prohibiting the compounds from working as needed. One with ordinary skill would be motivated to use these enteric coatings as it is noted by Huber et al. that the concept of using enteric coatings to protect drugs that are destroyed in gastric fluids is, of course, well known, and McCarthy et al. teach that other enteric coating agents can be used to protect the compound from degradation.. Shellac and cellulose acetate phthalate meet most of the criteria of a good enteric coating and they are among the most widely used coating materials for this purpose. These coatings are generally designed to pass the drug intact or in concentrated form through the stomach, and to deliver the drug to the more alkaline sites of absorption in the small and lower intestine.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over McCarthy et al. as cited supra, in view of Huber et al. as applied to claims 1-5, 7, and 8 above, and further in view of Ohno et al. (US Patent 4,017,647).

The Claims of the instant application are drawn to the composition as noted above, and additionally to using copolymers of methacrylic acid and acrylic acid esters, or copolymers of methacrylic acid and methacrylic acid esters as the encapsulation material.

The McCarthy et al. reference is incorporated into this rejection as set forth supra, in its entirety.

Ohno et al. teach of methods for producing enteric coatings which are soluble in the small-intestinal juice having a pH in the range of 4-8 (column 1, lines 57-66). Illustrative of the polymeric substances are (1) partial esters of at least one cellulose derivative having one or more substitution groups, such as, an alkyl cellulose (for example, methyl cellulose or ethyl cellulose), a hydroxyalkyl cellulose (for example, hydroxyethyl cellulose or hydroxypropyl cellulose), a hydroxyalkyl alkyl cellulose (for example, hydroxyethyl methyl cellulose, hydroxyethyl ethyl cellulose, or hydroxypropyl methyl cellulose), or cellulose esters (for example, cellulose acetate and cellulose acetate butyrate partially retaining hydroxyl groups of cellulose), with at least one polybasic acid, such as, succinic acid, maleic acid, phthalic acid, tetrahydrophthalic acid, hexahydrophthalic acid, trimellitic acid, or pyromellitic acid; (2) partial esters of at least one vinyl polymer or copolymer containing in its molecules vinyl alcohol units (for example, partially saponified polyvinyl acetate or polyvinyl acetoacetal) with at least one of the above-mentioned polybasic acids; (3) polymers of polymerizable monomers having carboxyl groups, such as, acrylic acid or methacrylic acid, or copolymers involving such a monomer unit; (4) polymeric substances convertible into the acid form by hydrolysis, such as, the polymers or copolymers of acrylic or methacrylic esters; and (5) polymers or copolymers prepared from monomers having carboxyl groups in the salt form, such as, sodium acrylate which are sodium

methacrylate and readily convertible into the acid form (column 1, line 67 – column 2, line 27). What Ohno et al. do not teach is to use FMdC as the active agent in the composition or the amounts of the compounds in the composition.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the various art recognized equivalent enteric coatings of Ohno et al. as the protective agent of Huber et al. to protect the FMdC composition of McCarthy et al. because Ohno et al. teach to use the protective agent of Huber et al. as well as the other various compounds which are claimed in the instant application as an enteric coating which allows for compounds to be dissolved in the slightly acidic pH of 4-8 of the intestine. One would be motivated to use the various enteric coatings of Ohno et al. for the compound of McCarthy et al. as these compounds would allow for the protection of FMdC from the acidic gastric juices in the stomach and allow for the dissolution of the compound in the intestine whereby becoming absorbed into the bloodstream.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Traviss McIntosh whose telephone number is 703-308-9479. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James O. Wilson
Supervisory Patent Examiner
Art Unit 1623

Traviss C. McIntosh
September 24, 2002